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C–N Bond Formation between Alcohols and Amines Using an Iron Cyclopentadienone Catalyst

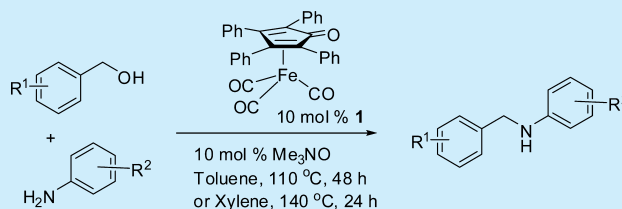
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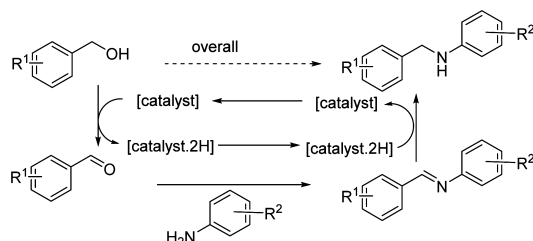
S Supporting Information

ABSTRACT: An iron-tetraphenylcyclopentadienone tricarbonyl complex is demonstrated to act as a precursor of a catalyst for the formation of C–N bonds through a “hydrogen-borrowing” reaction between amines and alcohols.



The development of sustainable methods for the formation of C–N bonds represents an important challenge for synthetic chemistry. One of the most promising methods involves the reaction between an amine and an alcohol, from which the only side product is a molecule of water.^{1–3} This process can be catalyzed by a number of organometallic complexes and involves a hydrogen transfer mechanism (Scheme 1) sometimes referred to as “hydrogen borrowing”.

Scheme 1. C–N Bond Formation via “Hydrogen Borrowing”



Although most commonly precious metal derivatives are employed in this process, it would be desirable to be able to use less expensive and/or more common metals such as iron.⁴

Iron cyclone complexes, including **1**–**3** (Figure 1), have been applied to alcohol oxidation and ketone reduction, including asymmetric versions.^{5–7} We recently extended our studies^{6,7} to the application of the same catalysts to C–N bond-formation reactions through a hydrogen-transfer process. At the time this work was undertaken, there was limited precedent for the use of iron catalysts for this transformation;⁸ however, a recent

article⁹ focused on the use of the Knölker complex **4** (the iron hydride formed in situ from **2**)¹⁰ has prompted us to report our results in this area.¹¹

In initial studies, the readily available iron cyclone complex **1** showed promise as a catalyst for the formation of C–N bonds in the reaction between benzyl alcohol **5** and aniline **6** to form amine **7** (Table 1). Using 10 mol % of **1** in toluene, with a 2-fold excess of benzyl alcohol, and trimethylamine-*N*-oxide to activate the catalyst,^{6,12} conversion to *N*-benzyl aniline **7** could clearly be observed and assayed by gas chromatography and ¹H NMR spectroscopy of the reaction.

Under these conditions, the conversion for the 48 h reaction was at least 99% provided an inert atmosphere was employed (entries 1 and 2). A reaction conducted in air gave <5% conversion to product (not shown) although ca. 40% imine was formed, indicating a significant level of aerial oxidation of the alcohol. Increasing the number of equivalents of alcohol did not significantly change the conversion, while reducing the alcohol below 1.5 equiv resulted in lower conversions. The conversion was almost complete after 24 h, and in xylene (140 °C) 98.6% of the required product was formed in 24 h. The conversion was significantly lower at 80 °C (5%), 90 °C (37%), and 100 °C (69%) after 48 h.

Although reactions were usually carried out in pressure tubes after degassing, they could also be conducted under reflux, without significant loss of yield. No coupling was observed in the absence of catalyst, or when an attempt was made to form the catalyst in situ by adding Fe(CO)₅, tetraphenylcyclopentadienone, and substrate together from the outset. Only 2% of product was formed when Fe(CO)₅ was employed alone as the catalyst. In contrast, however, it was possible to form a complex in situ in a separate step and then to add the amine and alcohol to this in order to achieve successful coupling (Table 1, entry 17). The use of 15 mol % of catalyst did not significantly

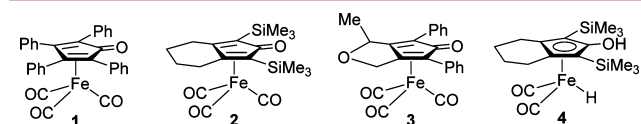
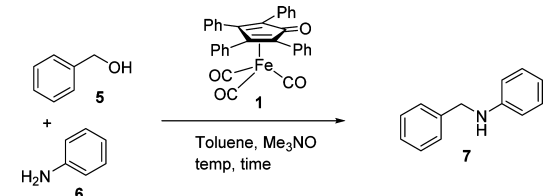


Figure 1. Iron cyclone complexes.

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Table 1. Coupling of Aniline and Benzyl Alcohol Using Catalyst 1^a


entry	mol % 1	equiv 5	temp (°C)	t (h)	convn (%)	imine (%)	N ₂ or Ar
1	10	2.0	110	48	99.0	1	Ar
2	10	2.0	110	48	99.8	0.2	N ₂
3	10	2.5	110	48	99.5	0.5	Ar
4	10	3.0	110	48	99.6	0.3	Ar
5	10	5.0	110	48	99.7	0.3	Ar
6	10	1.8	110	48	99	1	Ar
7	10	1.6	110	48	89	6	Ar
8	10	1.5	110	48	97	3	Ar
9	10	1.5	110	48	95	5	N ₂
10	10	1.3	110	48	81	7	N ₂
11	10	1.2	110	48	88	8	N ₂
12	10	1.1	110	48	78	7	Ar
13	10	1.1	110	48	89	8	N ₂
14	10	1.0	110	48	90	8	N ₂
15	10	2.0	110	24	94.4	0.3	Ar
16	10	2.0	140 ^b	24	98.6	0.6	N ₂
17	10	2.0	140 ^{b,c}	48	96	2	N ₂
18	15	2.0	110	48	98.8	0.2	N ₂
19	5	2.0	110	48	90.5	0.4	Ar
20	2	1.1	110	48	52	5	Ar
21	2	1.1	110	48	21	2	Ar

^a1.0 equiv of aniline, 1 equiv of Me₃NO relative to Fe complex, [aniline] = 0.5 M. ^bConducted in xylene. ^cCatalyst was first formed in situ by combination of dicyclopentadiene and Fe(CO)₅, and then addition of aniline and benzylalcohol. Conversion by mass recovery and GC ratio.

change the conversion, whereas it decreased slightly when only 5 mol % was employed, and significantly with just 2 mol % (Table 1, entries 18–21).

When benzylamine was employed as the amine partner, no product formation was observed. An attempted reaction between benzyl alcohol and aniline in the presence of 0.5 equiv of benzylamine also gave no coupling products, indicating that the benzylamine was inhibiting the catalyst. This may be due to the formation of a stable complex between the benzylamine and the activated catalyst (i.e., 8, Figure 2).

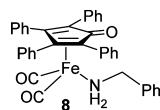


Figure 2. Iron cyclone complex with benzylamine.

is supported by the observation by Beller of deactivation of the corresponding Ru species by basic and unhindered amines.¹³ In contrast, aniline is insufficiently basic to strongly inhibit the catalysis by this mechanism.

Following optimization, we tested further combinations of aromatic amines with aliphatic alcohols using the optimized conditions (Scheme 2, Figure 3). The higher temperature

Scheme 2. Coupling of Aromatic Amines with Benzylamines Using Iron Tricarbonyl Complex 1

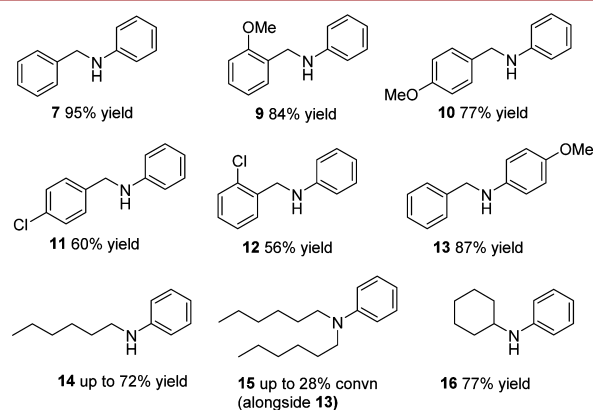
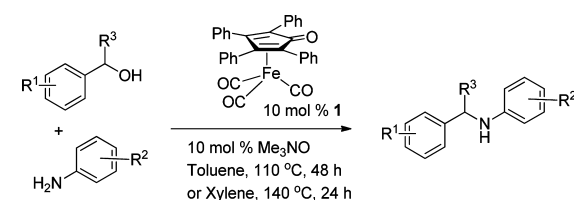


Figure 3. Products formed by coupling of aromatic amines with benzyl alcohols; 7 in toluene, 110 °C, 48 h, 9–16 in xylene, 140 °C, 24 h.

conditions were found to be efficient for the formation of the majority of the products. The reaction appears to tolerate changes to the benzyl alcohol, with products 9–12 all being formed in good conversion and subsequently isolated from the 140 °C/xylene reactions in the yields shown in Figure 3.

Variation of the arylamine was investigated with attempts at the coupling using *para*-methoxy-, *ortho*-methoxy-, *para*-chloro-, and *ortho*-chloroaniline. In the case of *para*-methoxyaniline, product 13 was obtained in 87% yield; however, products from the other amines (Figure 4) were formed in only

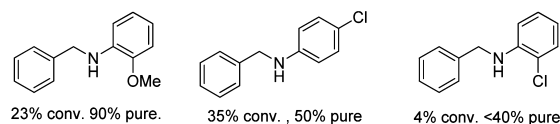


Figure 4. Substrates which worked poorly and were not isolated.

low conversions of 23%, 35%, and 4% respectively, and it was not possible to isolate purified products from these reactions (see Supporting Information for full details).

The reaction of aniline with hexanol gave up to 72% isolated product 14, although a quantity of dialkylated material 15 was also observed. Using just 1.1 equiv of hexanol, 67% of 14 was isolated without coformation of 15. However, all attempts to produce solely 15 by the use of excess hexanol (up to 3 equiv, for an extended reaction time of 48 h in xylene) gave at most 28% of conversion to 15, the majority being the monoalkylated 14. It is noteworthy that our findings for 14 and the other products match Feringa's⁹ in this respect; use of excess alcohol did not readily result in dialkylation. Likewise, attempts at the alkylation of secondary amines (*N*-methylaniline, pyrrolidine, cyclohexylmethylamine) were unsuccessful, yielding only traces of products even at the higher temperature of 140 °C. Attempts to couple aniline with α - and β -tetralol, and 1-phenylethanol, also resulted in only low conversions to impure products,

although the reaction with cyclohexanol did give a product, **16**, in 77% yield. Hence the reaction appears to be specific for certain classes of substrate, with a sharp dependence on the steric and electronic nature of the substituents on the reagents.

Traces of an imine intermediate were detected in the reaction mixtures at high conversion, and high levels of imine were observed at lower conversions (see Supporting Information). This supports the proposed “hydrogen borrowing” mechanism outlined in the introduction to this paper. Feringa has likewise found support for this mechanism in his work using a closely related catalyst.⁹ It is likely that the catalyst is first converted to the unsaturated species **17** through reaction with the trimethylamine oxide,^{6,12} and this subsequently forms the hydride **18** via reaction with the alcohol as shown in Figure 5. Although catalyst **1** is known to be capable of dehydrogen-

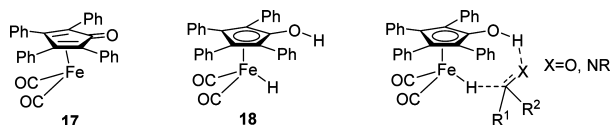


Figure 5. Activated and hydride derivatives of **1** and likely mechanism of hydride transfer.

ation of alcohols and of ketone reduction through intermediates **17** and **18**, the current application to “hydrogen borrowing” reveals a valuable new property of this class of catalyst.

Some comparison with the work of Feringa et al.⁹ is valuable at this point. Although our study was less comprehensive, we also observed the reluctance of the reaction to dialkylate the amine starting material, even when excess alcohol was used. While our experience was that benzylamine was not a suitable amine for coupling using **1** under our conditions, the catalyst used by Feringa et al., i.e. **4**, worked well with benzylic amines under their conditions. In our work, we focused on optimizations of reactions of aniline with benzyl alcohols, and were therefore able to form several derivatives in good yields. Our conditions appear to translate well in early tests to close reactions of other electron-rich anilines; for example the preparation of **13** in 87% yield. Further variation of the aniline structure however was not tolerated as well under our conditions as it was by Feringa et al.’s, although in both systems the yields of the ortho-substituted anilines were found to be lower than those for the para-substituted ones, possibly due to steric hindrance.

We believe that these results represent a valuable contribution to the area of C–N bond formation using sustainable metals and may find further use in the synthetic community. Further work is underway to establish the scope and applications of the catalyst system we have reported, as well as improvements to the catalyst structure and activity.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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